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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,375	10/09/2001	Donald Gerald Stein	07157/239838 (5543-17)	5877

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EXAMINER
JIANG, SHAOJIA A

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,375	STEIN ET AL.	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's response (Remarks) filed on December 19, 2003.

Currently, claims 1-20 are pending in this application.

Applicant's declaration of Dr. David W. Wright (not inventor), submitted December 19, 2003 under 37 CFR 1.132, is acknowledged and will be further discussed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gee et al. (Re. 35,517, of record) in view of Roof et al. (of record) further in view of Weinshenker et al. (5,068,226, of record) for the same reasons of record in the previous Office Action July 1, 2003.

Gee et al. discloses that progesterone metabolites and derivatives including the particular progesterone metabolite, allopregnanolone, are useful in a pharmaceutical compositions and method for modulating brain excitability via gamma-aminobutyric acid (GABA) (see particularly col.1 lines 17-21, Table 2 at col.13-14, col.4 lines 30-39,). Gee

et al. also discloses that the beneficial effect of progesterone is related to the conversion of progesterone to the active metabolites and derivatives including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone (see col.17 lines 29-35). Gee et al. also discloses the effective amounts of progesterone derivatives, either singly or *mixtures*, to be administered, i.e., 50 mg to 500 mg per dosage unit, within the instant claim, and various known pharmaceutical carriers broadly in the compositions. See col.9 lines 16-25 and 32-62, col.10 lines 2-3, and claims 1 and 5.

The prior art does not expressly disclose the employment of the particular progesterone metabolite, allopregnanolone, in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to the central nervous system (CNS), and administering allopregnanolone about 0.5 to about 100 hours following the traumatic CNS injury, or the first dosage -1 hour following the injury and second dosage –6 hours following the injury. The prior art does not expressly disclose the employment of cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone.

Roof et al. (43) discloses that progesterone possess ability to reduce significantly the cerebral edema associated with traumatic brain injury and facilitate cognitive recovery in a rat mammal. See the entire article especially abstract and introduction. Roof et al. (43) discloses particularly that "it is necessary that it be effective in reducing edema when given *after* the injury has occurred" (emphasis added originally, see page 64, the 2nd paragraph of the right column).

Roof et al. (44) discloses that progesterone has been shown to have neuroprotective effects following traumatic brain injury in rats, and/or in injured nervous system including the severity of postinjury cerebral edema. See the entire article especially abstract and introduction. Roof et al. also teaches that progesterone's neuroprotective effects are through its interaction with GABA, and progesterone and some of its metabolites are known to bind to and potentiate activity at the GABAa receptor (see page 7 the last paragraph). Roof et al. (43) discloses particularly that the initial treatment of progesterone by injection (4 mg/kg) was given 5 min post-injury and the remaining injections (4 mg/kg) were given 6 hour post-injury and again once each 24-hours (see page 4 the 3rd paragraph)

Roof et al. (45) discloses that progesterone is useful in the treatment of brain edema following contusion injury in male and female rats. See the entire article especially abstract and introduction. Roof et al. (45) discloses particularly that "it is necessary that peogesterone be effective in reducing edema when given *after* the injury has occurred" (emphasis added originally, see page 425, the 2nd paragraph of the right column).

Weinshenker et al. discloses that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone (see col.6 lines 20-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular progesterone metabolite,

allopregnanolone, in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to the central nervous system (CNS).

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular progesterone metabolite, allopregnanolone, in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to CNS, since progesterone is known to be useful in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to CNS according to Roof et al. Moreover, the particular progesterone metabolite, allopregnanolone, is known to be useful in a pharmaceutical compositions and method for modulating brain excitability via gamma-aminobutyric acid (GABA), and allopregnanolone is also known to possess higher potency and efficacy than progesterone has according to Gee et al. Further, progesterone and its metabolites such as allopregnanolone are known to share the same mechanism of action on their neuroprotective effects through their interaction with GABA, and progesterone and its metabolites are known to bind to and potentiate activity at the GABAa receptor according to Roof et al.

Therefore, one of ordinary skill in the art would have expected with a reasonable success that the particular progesterone metabolite, allopregnanolone, would be useful in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to CNS, because of having

the same therapeutic usefulness as progesterone in CNS and even exhibiting higher potency and efficacy, compared to progesterone.

Additionally, one having ordinary skill in the art at the time the invention was made would have been motivated to administer allopregnanolone about 0.5 to about 100 hours following the traumatic CNS injury, or the first dosage -1 hour following the injury and second dosage –6 hours following the injury, because the schedule or method for administering progesterone for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to the central nervous system (CNS) has been clearly taught by Roof et al. (43, 44, and 45). It has also been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Further, one having ordinary skill in the art at the time the invention was made would have been motivated to employ cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone since that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone according to Weinshenker et al.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments and Applicant's declaration of Dr. David W. Wright filed December 19, 2003 with respect to this rejection of claims 1-20 made under 35 U.S.C. 103(a) of record in the previous Office Action July 1, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

The declaration of Dr. David W. Wright under 37 CFR 1.132 has been fully considered but is ineffective to overcome the 103(a) rejections herein as to nonobviousness or unexpected results for the method of treating central nervous system injury herein over the prior art, since the declaration merely presents Dr. Wright's opinion or statements or conclusion regarding the claimed treatment herein and the cited prior art, but fails to set forth any factual evidences. Moreover, the declaration primarily discusses that the possible mechanism of action of the treatment proposed by Applicant is different from those of the cited prior art. Note that the mechanism of action of a treatment does not have a bearing on the patentability of the invention if the method steps are already known even though applicant has proposed or claimed the mechanism.

Thus, there is no clear and convincing evidence in the declaration for supporting the nonobviousness or unexpected results for the method herein over the prior art. Therefore, the declaration is insufficient to rebut the prima facie case herein.

Again, Applicant's argument that the possible mechanism of action of the treatment proposed by Applicant is different from those of the cited prior art, is not found

convincing. Note that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135,139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

Moreover, Applicant argues that the cited prior art fails to provide a reasonable expectation of success. Nonetheless, it is known that progesterone possess ability to reduce significantly the cerebral edema associated with traumatic brain injury and facilitate cognitive recovery in a rat mammal according to Roof et al. (43). Moreover, progesterone has been shown to have neuroprotective effects following traumatic brain injury in rats, and/or in injured nervous system including the severity of postinjury cerebral edema as taught by Roof et al. (44). Hence, a method of treating a traumatic central nervous injury broadly encompasses reducing cerebral edema associated with traumatic brain injury and facilitating cognitive recovery in a rat mammal. Thus, progesterone is known to be useful in a method of treating a traumatic central nervous injury in a patient.

Further, Allopregnanolone is also known to possess higher potency and efficacy than progesterone has according to Gee et al. Therefore, one of ordinary skill in the art would have expected with a reasonable success that the particular progesterone metabolite, allopregnanolone, would be useful in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to CNS, because of having the same therapeutic usefulness

as progesterone in CNS and even exhibiting higher potency and efficacy, compared to progesterone, absent evidence to the contrary.

As discussed in the previous Office Action July 1, 2003, Applicant's results shown in the Examples 1-7 of the specification at pages 20-40 herein have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention over the prior art but are not deemed persuasive for the reasons below.

It is noted that progesterone is employed in the testing of Example 6-7. Thus, Applicant clearly acknowledges that progesterone and its particular progesterone metabolite, allopregnanolone, have the same therapeutic usefulness as discussed by the examiner above. Therefore, Applicants' experiments further support the examiner's position for the motivation for the employment of allopregnanolone in the instant invention.

Secondly, the results in Examples 1-5 on the employment of the particular progesterone metabolite, allopregnanolone, show expected therapeutic effects as taught and suggested by the cited prior art herein. Therefore, the results herein are clearly expected and not unexpected based on the cited prior art. Expected beneficial results are evidence of obviousness. See MPEP § 716.02(c).

Therefore, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
April 13, 2004

SHAOJIA ANNA JIANG
PATENT EXAMINER